

AD

Award Number: W81XWH-14-1-0574

---

TITLE: Clinical Characterization and Imaging of Triggered Attacks in Chronic Migraine and Posttraumatic Headache

PRINCIPAL INVESTIGATORS: Peter Goadsby

CONTRACTING ORGANIZATION: University of California, Los Angeles  
Los Angeles, CA 90095

REPORT DATE: February 2016

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;  
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 222024302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. <b>PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.</b>					
1. REPORT DATE February 2016		2. REPORT TYPE Final Report		3. DATES COVERED 30 Sep 2015 - 20 Jun 2015	
4. TITLE AND SUBTITLE Clinical Characterization and Imaging of Triggered Attacks in Chronic Migraine and Posttraumatic Headache				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-14-1-0574	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Andrew Charles, M.D. and Peter Goadsby, M.D., Ph.D.				5d. PROJECT NUMBER PR130670	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Department of Neurology, UCLA School of Medicine 635 Charles Young Drive Los Angeles, CA 90095 Department of Neurology, UCSF School of Medicine 505 Parnassus Ave. San Francisco, CA 9143				7. PERFORMING ORGANIZATION REPORT NUMBER	
8. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				9. SPONSOR/MONITOR'S ACRONYM(S)	
				10. SPONSOR/MONITOR'S REPORT NUMBER(S)	
11. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
12. SUPPLEMENTARY NOTES					
7. ABSTRACT Chronic posttraumatic headache (PTH) is a disabling disorder that affects millions of individuals worldwide. The Principal Investigators (PIs) of this application proposed to develop human models of PTH by characterizing clinical features and correlated changes in brain activity before and during triggered attacks. The PIs hypothesized that the different headache triggers nitroglycerin (NTG) and prostaglandin E2 (PGE2) would produce different types of headache and would be associated with different patterns of brain metabolism that would reveal fundamental mechanisms of PTH. The studies were submitted for and achieved IRB approval at UCLA, and plans were in place to begin subject recruitment for the studies. However, because of administrative issues at UCSF (Dr. Goadsby's move leading to a change to a part-time appointment there), and because of an unexpected inability to obtain pharmaceutical grade PGE2, the actual research studies were not initiated, and the study has now been terminated. We are in the process of establishing a collaboration between UCLA and King's College London (the location of Dr. Goadsby's new position) and plan to move ahead with a similar but revised study once this formal collaboration is established. We will therefore continue to pursue the goals of this study in the future, but at this time the study is terminated.					
8. SUBJECT TERMS Post-traumatic headache, chronic migraine, PET, fMRI					
9. SECURITY CLASSIFICATION OF:			10. LIMITATION OF ABSTRACT	11. NUMBER OF PAGES	19a NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU		19b TELEPHONE NUMBER (include area code)

## Table of Contents

	<u>Page</u>
Introduction .....	4
Overall Project Summary .....	4-8
Key Research Accomplishments .....	8
Conclusion .....	9
Publications, Abstracts, and Presentations .....	9-12
Reportable Outcomes.....	12
Other Accomplishments.....	12-13
Appendices List .....	13

## **1. INTRODUCTION:**

The subject of the proposed research was the characterization of triggered attacks in patients with persistent post-traumatic headache (PTH). The purpose of the proposed research was to investigate basic mechanisms of PTH. The scope of the proposed research was to characterize clinical features and changes in brain metabolism associated with attacks of headache triggered by either nitroglycerin (NTG) or prostaglandin E2 (PGE2) using PET and fMRI approaches. The study was terminated early because of unforeseen administrative reasons.

## **2. KEYWORDS:**

Chronic migraine, post-traumatic headache, nitroglycerin, prostaglandin, positron emission tomography, functional magnetic resonance imaging.

## **OVERALL PROJECT SUMMARY:**

### **Task 1. Recruitment and clinical characterization of patients with persistent post-traumatic headache for study (Months 1-30)**

#### **a. Obtain IRB approval for recruitment of patients and data collection (Month 1-2)**

*This task was completed, including development of an approved protocol and infrastructure for performance of the study.*

#### **b. Recruitment of patients for study and screening for inclusion and exclusion criteria (Months 3-30).**

*No patients were formally recruited for the study*

#### **c. Enrollment of subjects with informed consent (Months 3-32).**

*No patients were enrolled in the study*

### **Task 2. Characterization of the clinical responses to nitroglycerin (NTG) in patients with persistent posttraumatic headache (Months 3-36)**

#### **a. Perform detailed recording of premonitory symptoms, headache, and postdromal symptoms in subjects following intravenous administration of nitroglycerin (Months 3-36)**

*Dr. Goadsby carried out related studies in patients with chronic migraine (in a separate project), but did not perform any of the specific studies proposed here.*

#### **b. Characterize response of triggered symptoms to therapy with subcutaneous sumatriptan (Months 3-36)**

*These studies were not performed*

**Task 3. Characterization of the clinical responses to prostaglandin E2 in patients with persistent posttraumatic headache (Months 3-36)**

**a. Perform detailed recording of premonitory symptoms, headache, and postdromal symptoms**

**in subjects following intravenous administration of prostaglandin E2 (Months 3-36)**

**b. Characterize response of triggered symptoms to therapy with subcutaneous sumatriptan**

*These studies were not performed, in part because pharmaceutical grade PGE2 became unavailable after the study was approved.*

**Task 4. Functional brain imaging of NTG-triggered attacks in patients with persistent posttraumatic headache (Months 6-36)**

**a. Perform 18-fluorodeoxyglucose (FDG) PET scans during a NTG-triggered attack and on a separate occasion at baseline at least 1 week prior to or after triggering session in patients with persistent posttraumatic headache. (Months 6-36)**

**b. Perform a baseline anatomical and resting-state functional MRI in the same subjects at the same time as the baseline PET scan. (Months 6-36)**

**c. Compare patterns of brain metabolism at baseline and during triggered attacks. (Months 6- 36)**

*These studies were not performed*

**Task 5. Functional imaging of PACAP-triggered attacks in patients with persistent posttraumatic headache (Months 6-36)**

**a. Perform 18-FDG PET during a PACAP-triggered attack and on a separate occasion at baseline at least 1 week prior to or after triggering session in patients with persistent posttraumatic headache. (Months 6-36)**

**b. Perform a baseline anatomical and resting-state functional MRI in the same subjects at the same time as the baseline PET scan. (Months 6-36)**

**c. Compare patterns of brain metabolism at baseline and during triggered attacks (Months 6-36)**

*These studies were not performed*

**Task 6. Comparison of baseline brain connectivity and metabolism between patients with persistent posttraumatic headache and normal controls (Months 12-36).**

*None of these studies were performed.*

#### **4. KEY RESEARCH ACCOMPLISHMENTS**

IRB approval for triggered attack studies in patients with persistent post-traumatic headache was achieved at UCLA. Development of an infrastructure for future collaborative studies with Dr. Goadsby on clinical characterization and imaging of patients with PTH.

#### **5. CONCLUSION:**

The study was terminated early due to unforeseen administrative issues

#### **6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:**

**Publications** None

**Abstracts** None

**Invited Presentations** None

**7. Inventions, patents and Licenses** None

**8. Reportable Outcomes** None

#### **9. Other Achievements**

Establishment of a collaboration with Amgen for future studies of pathophysiology and therapy of chronic post-traumatic headache.

**10. REFERENCES** None

**11. APPENDICES:** None